

FINAL REPORT

Detection and evaluation of early functional alterations in vasculature is one of the most important research topic in the clinical cardiology. At this moment only a limited number of clinically useful method is available for the assessment of vascular arterial function. In our cardiology center, the following clinical methods are used:

- echocardiography-derived coronary flow reserve (CFR)
- echocardiographically measured aortic stiffness parameters including aortic strain, distensibility, stiffness index, elastic modulus and Young's circumferential static elastic modulus
- pulse wave velocity and augmentation index evaluated by Arteriograph (a tool based on oscillometry).
- videodensitometric myocardial perfusion and blush parameters (Gmax/Tmax) assessed on coronary angiograms.

All these parameters can be used in clinical practice, but their diagnostic and prognostic role need further evaluations. Regarding to our working plan it was aimed to examine these functional arterial parameters (alone and in combination) in cardiac and noncardiac patients. Moreover, it was also aimed to examine if there is any relationship between these parameters. We focused on patients without coronary artery disease (in most of cases confirmed by coronary angiography with a negative result), but other special patient populations were also examined (for instance hypertrophic cardiomyopathy, acromegaly, lipoeedema etc.).

As we planned clinical, demographic, arteriographic, coronary angiographic and myocardial blush data of hundreds of patients have been collected regarding to the possibilities and clinical needs following our working plan. Data have been inserted into excel files, completed and analysed by statistical methods. There wer no changes in research personel during the project.

The studies

Coronary flow reserve (CFR) follow-up studies (SZEGED Study)

From 1997, hundreds of CFR examinations have been performed at the 2nd Department of Medicine and Cardiology Center, University of Szeged, Hungary to clarify its diagnostic value. Regarding to our working plan, it was aimed to assess the very long-term prognostic impact of CFR in special patient populations. This study was named after SZEGED (SummarizatiON of long-tErM prognostic siGnificance of coronary flow rEserve in special Disorders):

- Previously, the prognostic role of CFR was found in patients with left anterior descending coronary artery (LAD) stenosis. Recently, we have demonstrated the prognostic significance of CFR for prediction of mortality in patients with coronary artery disease not involving the LAD during a 9-year follow-up. This fact is very interesting, because CFR measurement were made in the LAD, but macrovascular alterations could be demonstrated only in the other coronaries (left circumflex and right coronaries) during coronary angiography.

Presented: EUROECHO2009 Congress (2009. december, Madrid, Spain)

Published in Echocardiography. 2010; 27(3): 306-310.

- Moreover, it was possible to demonstrate the prognostic role of CFR for prediction of cardiovascular morbidity and mortality in patient with aortic valve stenosis (AS), as well. AS is a valvular disease, which is frequently associated with different vascular alterations. That paper was the first to demonstrate that CFR as a functional vascular parameter is a strong predictor of future cardiovascular events in these patients.

Presented: EUROECHO2009 Congress (2009. december, Madrid, Spain) and at the Congress of the Hungarian Society of Cardiology (2010. May, Balatonfüred, Hungary)

Published in Clin Physiol Funct Imaging. 2009; 29(6): 447-452.

- During a 10-year follow-up in female patients with chest pain and negative coronary angiograms, abnormal LAD-CFR was found to be a strong and independent predictor of cardiovascular outcome. It is known, that coronary artery disease is the leading cause of death in women, but clinical picture of coronary heart disease in women is often different than that in men, evidence of a particular pathophysiology: it is most often identified when acute, as non-ST-elevated acute coronary syndrome, and

involves a higher frequency than among men of normal coronary arteries, microvascular damage, and endothelial dysfunction.

Presented: EUROECHO2010 Congress (2010. december, Copenhagen, Denmark).

Published in Int J Cardiol. 2011; 146(2): 259-261.

- Diabetes mellitus (DM) is an important predictor of cardiovascular events in patients with and without coronary artery disease. We organized a study to examine whether cardiovascular outcome can be predicted by Doppler echocardiography-derived CFR even in non-diabetic patients with chest pain and negative coronary angiograms. We found that after exclusion of factors affecting CFR as DM, which is one of the most important causes of microvascular disease and significant macrovascular stenoses by coronary angiography, CFR still remains a strong predictor of future events.

Presented: 19th Alpe-Adria Cardiology Meeting (2010. september, Vienna, Austria) and EUROECHO2010 Congress (2010. december, Copenhagen, Denmark).

The manuscript has been submitted.

- The prognostic value of CFR for prediction of cardiovascular outcome has even been found in patients without LAD stenosis. It was a mixed patient population including subjects without macrovascular coronary artery disease and cases with left circumflex and/or right coronary disease.

Presented: Heart Failure2010 Congress (2010. May, Berlin, Germany).

Published in Orv Hetil. 2010; 151(9): 338-343.

Evaluation of aortic stiffness parameters in healthy volunteers and in patients with special diseases

- Two different methods characterizing aortic stiffness were compared in our center in considering the facts that there are now two different ways to evaluate aortic distensibility: measuring pulse wave velocity (PWV) and augmentation index (AIx) by oscillometry-based Arteriograph or calculating a modulus or index, in which changes in blood pressure and aortic size (by Echocardiography) during a cardiac cycle are considered. The measurement of PWV and AIx by Arteriograph is a new emerging tool; it has just been validated against broadly accepted tonometric and piezoelectronic methods finding the best for variability and reproducibility for PWV. With the present validation study we have found significant correlations between Arteriograph-derived

PWV and AIx and aortic elastic properties determined by echocardiography in healthy volunteers.

Presented: EUROECHO2009 Congress (2009. december, Madrid, Spain)

Published in Clin Physiol Funct Imaging. 2011; 31(1): 61-65.

- Moreover, using five aortic elasticity parameters (PWV, AIx and three echocardiographic elastic properties) by two different methods (echocardiography, Arteriograph), correlations could be demonstrated between aortic elasticity and vegetative parasympathetic autonomic function, as assessed by standard cardiovascular reflex tests in healthy volunteers. These results could highlight attention on the effect of autonomic function on arterial system even in healthy subjects.

Published in Can J Physiol Pharmacol. 2010; 88(12): 1166-1171.

- The relationship between insulin sensitivity and aortic stiffness is an interesting physiologic problem. We found a correlation between these factors even in subjects with normal carbohydrate metabolism.

Presented: Congress of the Hungarian Society of Cardiology (2010. May, Balatonfüred, Hungary)

- Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disease caused by a variety of mutations in genes and defined by the presence of unexplained left ventricular hypertrophy with a varied clinical course and outcome. Vascular alterations are frequently associated with HCM including microvascular and/or peripheral endothelial dysfunction. Our results were the first to demonstrate abnormal echocardiographic aortic elastic properties and Arteriograph-derived PWV in HCM patients as compared to matched controls.

Presented: EUROECHO2010 Congress (2010. december, Copenhagen, Denmark)

Published in Cardiologia Hungarica 2011; 41: 9-13 and another manuscript has been submitted.

- Regarding to our aims, other special patient populations were also examined. In cooperation with (former) Department of Endocrinology, aortic stiffness were examined first time in patients with acromegaly and found to be increased in 2005. In a recent follow-up study, echocardiography-derived aortic stiffness index was found to be an independent predictor of future cardiovascular events in acromegalics.

Published in Int J Cardiol. 2011; 147(3): 457-459.

- Lipoedema is a disproportional obesity, that nearly always affects women and is characterized by bilateral, symmetrical, biker's hosiery-shaped fatty swelling of the legs with sparing of the feet. Its major hallmark is frequent hematoma formation due to increased capillary fragility and reduced venoarterial reflex. Beyond microangiopathy, venous and lymphatic dysfunctions have also been detected. Our study has clearly shown that aortic stiffness is increased in lipoedematous patients compared to healthy individuals within similar age group suggesting early vascular remodelling.

The manuscript has been submitted.

The evaluation of the relationship between aortic stiffness and CFR

- CFR and echocardiography-derived aortic elastic properties were examined in patients with different kinds of single-vessel coronary artery disease (SVD) with vs. without diabetes mellitus. As a result it could be concluded that diabetes mellitus reduces CFR only in non-LAD-SVD patients and impairs already decreased aortic elasticity in SVD regardless of stenosis location.

Published in Diabetes Res Clin Pract. 2009; 86(2): e41-42.

- It is known that CFR improves after successful percutaneous coronary intervention (PCI) of LAD stenosis, and CFR early after PCI has been reported to be of good prognostic value in predicting patients requiring reintervention. Recently, a limited number of papers confirmed the additive effect of invasive procedures such as aortic valve replacement, aortic full root replacement, and the Ross procedure on aortic elasticity improvement. The results of our study showed that the CFR and aortic distensibility indices can be evaluated serially by means of echocardiography. Moreover, as far as we are aware, it was the first demonstration that the aortic distensibility improves in parallel with an increase in the CFR in patients with LAD stenosis after successful PCI.

Published in Echocardiography. 2010; 27(3):311-316.

- Moreover, it could also be demonstrated that echocardiographically evaluated aortic elastic modulus could predict reduced CFR. In this clinical study higher grade of aortic atherosclerosis as a morphologic characteristic and increased aortic elastic modulus (as a functional parameter) could be demonstrated as independent predictors of reduced CFR.

Presented: Congress of the European Society of Cardiology (2010. september, Stockholm, Sweden)

The manuscript has been submitted.

Videodensitometric studies

Methods for computerized videodensitometric analysis of digital subtraction coronary angiograms have been reported. The primary goal of these studies was to develop an operator-independent and quantitative way of myocardial perfusion assessment based on X-ray coronary angiograms, which is the only imaging modality widely available during coronary interventions. A novel computerized videodensitometric method has been introduced some years ago and used in our practice to examine its diagnostic and prognostic role. The computerized method for myocardial perfusion assessment was based on the analysis of time–density curves (TDCs). Maximal density of the TDC (Gmax) and time to reach maximal density (Tmax) were measured on the filtered curve. Gmax/Tmax ratio was used as a characteristic of myocardial blush of selected myocardial areas. During our examinations, alterations in myocardial perfusion parameters could be demonstrated in hypertensive patients with normal epicardial coronary arteries and in elderly subjects with negative coronary angiograms compared to matched controls.

Presented: Congress of the European Society of Cardiology (2010. september, Stockholm, Sweden) and Congress of the Hungarian Society of Cardiology (2010. May, Balatonfüred, Hungary).

Moreover, a relationship was assessed between myocardial blush parameters and TIMI frame count (TFC). TFC defined as the number of frames required for contrast material to travel from the coronary ostium to a distal landmark was introduced in the early 1990s, as a method to assess the efficacy of thrombolysis and risk stratification in acute myocardial infarction (AMI). TFC proved to be a simple, reproducible, quantitative and objective method to evaluate epicardial flow not only in acute coronary syndrome settings, but in conditions with microvascular dysfunction, as well. Significant correlations could be demonstrated between computerized videodensitometric myocardial blush assessments and quantitative coronary angiographic corrected TFC method characterizing myocardial flow in patients without significant coronary artery stenosis.

The manuscript has been submitted.

Invasive measurement of CFR in patients with coronary artery - heart chamber fistulas

Coronary fistulas to one of the cardiac chambers are infrequent anomalies and usually are found unexpectedly. As a complementary examination, we found alterations in invasively measured CFR in a patient with multiple coronary fistulas originating from all major coronary arteries and in a patient with LAD-pulmonary artery fistula. These are the first demonstrations of the usefulness of CFR measurement for the evaluation of functional significance of coronary fistulas.

Published in Acta Cardiol. 2010; 65(3): 357-360

The other manuscript has been submitted.

Over the above mentioned congresses, I have participated in the conference of the American Heart Association in 2010 (Chicago, USA).